NOT FOR PEER REVIEW

KEY PAPER EVALUATON

Tesofensine – a novel potent weight loss medicine

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1. **Introduction**
2. **Methods and results**
3. **Discussion**
4. **Expert opinion**

Abstract *Background* The incidence of obesity is increasing and this is of major concern as obesity is associated with cardiovascular disease, stroke, type 2 diabetes, respiratory tract disease, and cancer. *Objectives/Methods* This evaluation is of a Phase II clinical trial with tesofensine in obese subjects. *Results* After 26 weeks, tesofensine caused a significant weight loss, and may have a higher maximal ability to reduce weight than the presently available anti-obesity agents. However, tesofensine also increased blood pressure and heart rate, and may increase psychiatric disorders. *Conclusions* It is encouraging that tesofensine 0.5 mg may cause almost double the weight loss observed with sibutramine or rimonabant. As tesofensine and sibutramine have similar pharmacological profiles, it would be of interest to compare the weight loss with tesofensine in a head-to-head clinical trial with sibutramine, to properly assess their comparative potency. Also, as tesofensine 0.5 mg increases heart rate, and the incidence of adverse effects such as nausea, drug mouth, flatulence, insomnia, and depressed mode, its tolerability needs to be further evaluated in large Phase III clinical trials.

Key words clinical trial, obesity, sibutramine, tesofensine

1. Introduction

The incidence of obesity is increasing worldwide, and in the US, about 100 million adults are overweight or obese. Comorbidities with obesity include cardiovascular disease (e.g. hypertension, coronary artery disease, left ventricular hypertrophy), stroke, Type 2 diabetes, respiratory tract disease (e.g. obstructive sleep apnoea, increased infections, asthma) and cancers. In 40-year-old male and female nonsmokers, it has been suggested that obesity shortens life expectancy by 5.8 and 7.1 years, respectively [1]. Orlistat and sibutramine are among the drugs presently used for weight loss, but they both have a relatively modest effect. The clinical development of the cannabinoid receptor antagonist rimonabant for the treatment of obesity has recently been stopped due to safety concerns [2]. Thus, the search for safe, effective and potent anti-obesity drugs continues.

In development for Parkinson's and Alzheimer's disease, tesofensine was shown to reduce body weight [3]. In the total cohort of 740 patients treated with tesofensine, over 14 weeks, the weight loss was -0.9%, -1.8%, and -2.8% with tesofensine 0.25, 0.5 and 1.0 mg, respectively, compared to +0.5% in the placebo group of 228 patients [3]. Weight loss with tesofensine was similar or slightly higher in the obese subgroup; -1.6%, -1.5% and -3.7% with tesofensine 0.25, 0.5 and 1.0 mg, respectively, compared to -0.2% in the placebo group [3]. Tesofensine 0.25, 0.5 and 1 mg increased heart rate by 4.2, 6.0 and 6.8 beats/minute, respectively, without altering blood pressure [3]. As a result of this information, a clinical trial of tesofensine in obesity was undertaken, and is evaluated here.

2. Methods and results

The methods and results of the Phase II, randomised, double-blind, placebo-controlled trials showing weight loss with tesofensine [4] are combined in this section. The trial was undertaken in 5 Danish obesity management centres, and recruited obese subjects (body mass index, BMI from 30 to less than 40 kg/m^2) from 18 to 65 year olds. There were many exclusion criteria including cardiovascular disease, abnormalities in the electrocardiogram, uncontrolled hypertension, and heart rate of > 90 beats/min.

The 203 obese subjects enrolled were predominantly women (~70%), almost all white, with a mean BMI of ~35 kg/m^2, and waist of ~110 cm. During a 2-week dietary run-in period and during the study, a diet with a daily energy deficit of 300 kcal was recommended, as was an increase in physical activity to 30-60 minutes/day. Subjects were randomised to placebo or tesofensine at 0.25, 0.5, and 1 mg orally for 24 weeks. Subjects attended dietician clinics weekly for 4 weeks, and then every second week. Withdrawals in the placebo, tesofensine 0.25, 0.5 and 1 mg groups were of 13, 9, 6, and 14 people.

The primary efficacy endpoint was percent change in body weight, and this was 2.0% in the placebo group over 26 weeks. There was an addition loss of 4.5% (4.5 kg), 9.2% (9.1 kg), and 10.6% (10.6 kg) in the tesofensine 0.25, 0.5, and 1 mg groups, respectively. After discontinuation of treatment for 8 weeks, there was a weight gain of 0.5% in the placebo group, and bigger gains of 0.8%, 2.3%, and 3.8% in the tesofensine 0.25, 0.5 and 1 mg groups, respectively.

At 26 weeks, all 3 doses of tesofensine also lowered body fat and waist circumference, and decreased total cholesterol to a small extent, but had no significant effect on LDL cholesterol or HDL cholesterol levels. Tesofensine 0.5 and 1.0 mg lowered the levels of triglycerides. Tesofensine had no effect on plasma glucose, but at 1 mg lowered glycosylated haemoglobin.

Heart rate increased by 4.7, 7.8 and 8.5 beats/min in the tesofensine 0.25, 0.5 and 1 mg, groups, which was significantly higher than the 0.4 beats/min in the placebo group. The two lower doses of tesofensine had no significant effect on blood pressure, but tesofensine 1 mg increased blood pressure by 6.8/5.8 mm Hg, compared to 1.3/1.5 mm Hg in the placebo group.

The profile of mood states (POMS brief) was completed at baseline and after weeks 12 and 24. This brief tests six mood factors; tension-anxiety, depression-dejection, anger-hostility, vigour-activity, fatigue-inertia, and confusion-bewilderment. Tesofensine did not alter mood overall, but at I mg increased anger and hostility, and at 0.5 and I mg increased confusion. Tesofensine also improved vigour and activity.

The improvement of total weight-related quality of life-lite (IWQOL-Lite) measures 5 domains: physical function, self-esteem, sexual life, public distress, and work. The

IWQOL-Lite was improved by 3% by placebo, and this was increased to 17% with tesofensine 0.25 mg, and to 21% by tesofensine at both 0.5 mg and 1 mg.

There was no excess of serious adverse effects, but there was an excess of adverse effects with tesofensine. Thus, serious adverse events occurred in 8% of placebo subjects, and in 4%, 2% and 6% of subjects treated with tesofensine 0.25, 0.5 and 1.0 mg, respectively. Whereas, excess adverse effects with all doses of tesofensine included nausea, dry mouth, hard faeces, insomnia, and palpitations. Nausea was observed in 9.6% of subjects in the placebo group, and this was increased to 17.3%, 20.0%, and 22.4% with tesofensine 0.25, 0.5 and 1 mg, respectively. Dry mouth was observed in 11.5% of the placebo group, but in 23.1%, 42.0% and 59.2% of subjects with tesofensine 0.25, 0.5 and 1 mg, respectively. Insomnia was observed in 1.9% of placebo subjects, and this was increased to 3.8%, 12.0% and 26.5% by tesofensine 0.25, 0.5 and 1 mg, respectively. In addition, the highest dose of tesofensine (1 mg) increased the incidence to abdominal pain (placebo, 0%; tesofensine, 12.2%), constipation (7.7% vs 16.3%), sleep phase rhythm disturbances (3.8% vs 12.2%), and depression (mood depression and major depression) (0% vs 8.1%).

3. Discussion

The authors point out that the lowest dose of tesofensine 0.25 mg causes a greater weight loss than orlistat, and a similar weight loss to sibutramine and rimonabant [4]. Tesofensine 0.5 mg causes twice the weight loss observed with sibutramine and rimonabant [4]. However, the authors do concede that their study is a relatively small Phase II study, and that the comparative results need to be borne out by a larger Phase III studies, including direct comparison studies [4]. The authors also suggest that tesofensine has a lesser effect on blood pressure and heart rate than sibutramine for a comparable weight loss [4]. The discussion ends with “We conclude that tesofensine 0.5 mg, once daily for 6 months, has the potential to produce twice the weight loss as currently approved drugs: however, larger phase III studies are needed to substantiate our findings”.

4. Expert opinion

4.1 Safety of tesofensine in subjects with cardiovascular disease

Subjects with cardiovascular disease were excluded from this Phase II trial. Thus, the safety of tesofensine in subjects with cardiovascular disease has not been

established. As cardiovascular disease commonly co-exists with obesity, it may be appropriate to test tesofensine 0.5 mg in subjects with obesity and mild cardiovascular disease (e.g. controlled hypertension) in a Phase II trial with extensive cardiovascular monitoring, prior to any Phase III trials.

4.2 Mechanisms of action of tesofensine and sibutramine

Tesofensine is described in clinical trials as an inhibitor of the reuptake of noradrenaline, dopamine, and 5-hydroxytryptamine [4,5]. The reference for this combination of mechanisms is Thatte (2001), who states "NS-2330 is believed to increase the activity of dopamine, norepinephrine and acetylcholine by inhibiting the re-uptake of the monoamines (dopamine, norepinephrine and serotonin)", but there is no associated reference or evidence to support this [5]. Subsequently, tesofensine and its metabolite M1 have been shown to inhibit dopamine uptake with EC_{50} values of 72 nM and 363 nM, respectively [6]. Unpublished data discussed by Lehr et al [6] suggests that tesofensine and its metabolite M1 inhibit noradrenaline uptake with IC_{50} values of 1.7 nM and 0.6 nM, and 5-hydroxytryptamine (5-HT) uptake with IC_{50} values of 11 nM and 2nM, respectively. This shows that tesofensine shows some selectivity in inhibiting noradrenaline and 5-HT uptake over dopamine uptake. Sibutramine also shows selectivity in inhibiting noradrenaline and 5-HT over dopamine uptake [7]. Thus, it seems to me, that tesofensine will have very similar effects to sibutramine in clinical trial for obesity, and this is borne out by the results of the Phase II trial with tesofensine. Although the authors of the Phase II trial with tesofensine are suggesting that it causes a similar loss of weight to sibutramine for a lesser effect on blood pressure and heart rate, given the similarities in mechanisms of action, it will be interesting to see whether this is substantiated in Phase III trial. The ideal Phase III clinical trial would be a direct comparison of tesofensine and sibutramine.

4.2 Psychiatric disorders

In the individual large Rimonabant in Obesity (RIO) clinical trials, there was not an increase in psychiatric disorders with rimonabant, but when the trials were combined, it was shown that rimonabant caused a small increase in the incidence of anxiety and depression [8], which ultimately led to the decision of the manufacturer Sanofi-Aventis to stop the clinical development of rimonabant for the treatment of obesity [9]. In the small Phase II trial evaluated here, depressed mood did not occur in the placebo group, but was observed in 1.9%, 6.0% and 6.1% of the subjects taking tesofensine, 0.25, 0.5 and 1 mg, respectively [4]. Major depression was observed in

one subject taking tesofensine, 1 mg [4]. Large Phase III clinical trials are indicated to determine whether tesofensine, like rimonabant, causes unacceptable levels of psychiatric disorders.

4.3 Effects on cholesterol levels

Tesofensine had no effect on LDL cholesterol levels. The authors of the Phase II study compare this with sibutramine and rimonabant, which also have no effect on LDL cholesterol [4]. However, the authors failed to mention, that orlistat does decrease LDL cholesterol levels [e.g. 10], and that this is an advantage with orlistat over sibutramine, rimonabant and tesofensine.

4.4 No future for tesofensine 1 mg in weight management

Although tesofensine 1 mg caused a greater weight loss than tesofensine 0.5 mg (10.6 kg vs 9.1 kg), this came at the expense of additional adverse effects (abdominal pain, constipation, sleep phase rhythm disturbances, and depression) and an appreciable rise in blood pressure and heart rate. These additional adverse effects and cardiovascular effects of tesofensine 1 mg are likely to preclude future development of this dose for the treatment of obesity.

4.5 Conclusions

It is encouraging that tesofensine 0.5 mg may cause almost double the weight loss observed with sibutramine or rimonabant. The safety of tesofensine in subjects with cardiovascular disease has not been established, and should be tested in Phase II. As tesofensine and sibutramine have similar pharmacological profiles, it would be of interest to compare the weight loss with tesofensine in a head-to-head clinical trial with sibutramine, to properly assess their comparative potency. Also, as tesofensine 0.5 mg increases heart rate and the incidence of adverse effects such as nausea, drug mouth, flatulence, insomnia, and depressed mode, its tolerability needs to be further evaluated in large Phase III clinical trials.

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